CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206089Orig1s000

STATISTICAL REVIEW(S)

MEMORANDUM OF STATISTICAL REVIEW

NDA #:	206089 (Supporting Document 061 / eCTD # 0060)
Product Name:	Testosterone undecanoate
Indication(s):	Treatment of male hypogonadism
Applicant:	Clarus Therapeutics, Inc.
Dates:	September 27, 2018 PDUFA Date: March 27, 2019
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Sonia Castillo, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Clinical Reviewer: Debuene Chang, M.D. Clinical Team Leader: Mark Hirsch, M.D.
Project Manager:	Jeannie Roule

This Class 2 resubmission consists of the sponsor's response to the March 22, 2018 Complete Response Letter and five clinical pharmacology study reports. These five clinical pharmacology studies do not require statistical review of efficacy. There are no statistical efficacy issues that would preclude approval.

Reference ID: 4396841

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/s/

SONIA CASTILLO
02/27/2019 05:01:22 PM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Supporting Doc. #:	206089 / 31 (eCTD Sequence # 0030)
Drug Name:	Oral Testosterone Undecanoate
Indication:	Treatment of adult male hypogonadism
Applicant:	Clarus Therapeutics, Inc.
Date(s):	Letter Date: June 22, 2017 PDUFA Date: March 22, 2018
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
Concurring Reviewer:	Mahboob Sobhan, Ph.D.
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Key Words: Clinical studies, NDA review

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Reference ID: 4221052

1. EXECUTIVE SUMMARY

The one submitted study provides evidence demonstrating the efficacy of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism. The evidence is based on achieving plasma total testosterone levels within the normal range at study end in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the proportion of men achieving the plasma total testosterone levels within the normal range no less than 65%. The normal range of plasma total testosterone level for this product is defined as ≥ 252 ng/dL and ≤ 907 ng/dL. The percentage of men with a plasma total testosterone level within the normal range at study end was 87.3% (145 of 166 subjects) with 95% confidence interval of 81.3% to 92.0%.

2. INTRODUCTION

2.1 Overview

This submission consists of one open-label, active control (for safety), parallel group, dose titration, multicenter study to evaluate the efficacy and safety of oral testosterone undecanoate (TU) capsules for the treatment of adult male hypogonadism. Table 2.1 presents a brief study summary.

Table 2.1
Brief Summary of Clinical Study for Testosterone Undecanoate (TU)

Study Number (Country / #) Dates of Study Conduct	Subject Population	Treatment[1]	ITT[2] Population	Design[3]
CLAR-15012 (United States / 31) March 2016 to Nov 2016	Men aged 18 to 65 years with clinically diagnosed hypogonadism (total serum testosterone levels < 300 ng/dL)	Oral TU (daily BID dose: 158 mg, 198 mg, 237 mg, 316 mg, or 396 mg) Axiron (daily QD dose: 30 mg, 60 mg, 90 mg, or 120 mg) **Total**	166 56 **222**	OL,AC (for safety), PG, DT, MC, at least 105 days

Source: Statistical Reviewer's listing.
[1] BID = Twice Daily, QD = Once Daily
[2] ITT = Intent to Treat
[3] OL = Open-label, AC = Active Control, PG = Parallel Group, DT = Dose Titration, MC = Multicenter

The proposed indication is:

Testosterone undecanoate capsules are indicated for the treatment of adult male hypogonadism.

The proposed dose of testosterone undecanoate is 158 mg, 198 mg, 237 mg, 316 mg, or 396 mg twice daily.

2.2 Data Sources

The application was submitted electronically. The submitted SAS data sets were complete and well documented. The following review items are located in the CDER Electronic Document Room as described below:

- The complete study report was submitted under submission date 6-22-2017 (SDN 31 / eCTD Sequence Number 0030) which is located at \\CDSESUB1\evsprod\NDA206089\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\male-hypogonadism\5351-stud-rep-contr\clar-15012 .
- Raw and derived data sets used for analysis and the data set define and program files are located at \\CDSESUB1\evsprod\NDA206089\0000\m5\datasets\clar-15012 under submission date 6-22-2017 (SDN 31 / eCTD Sequence Number 0030)

3. STATISTICAL EVALUATION

This section describes the study design, data and analysis quality, evaluation of efficacy, and study results. Although Axiron was included in this study as an active comparator, its purpose was for safety reasons and will not be further discussed in this statistical review of efficacy for oral TU and defer to the clinical reviewer's report for further information on the safety.

3.1 Data and Analysis Quality

The submitted datasets were well documented and easily accessible. The derived efficacy datasets used for the primary efficacy analysis can be created from the raw datasets. I reproduced the primary efficacy results as presented in the study report from the derived efficacy dataset based on frequency of events.

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There was one change to the primary efficacy analysis; the plasma total testosterone normal range presented in the first version of the protocol was changed from ≥ 300 ng/dL and ≤ 1000 ng/dL (which is typically used for serum total testosterone) to ≥ 252 ng/dL and ≤ 907 ng/dL. This change was made prior to completion of the study (under IND 78104 supporting document 102 dated 11-25-2016) and was found acceptable by the clinical pharmacology review team. Otherwise, there were no other changes to the pre-specified primary analyses.

There was one issue identified that may have affected the quality of the efficacy analysis. The Applicant changed the laboratory used to assay the plasma total testosterone concentrations after they discovered that the original laboratory produced unreliable concentration values. These concentration values are used to determine the plasma total testosterone C_{avg} used in the primary efficacy evaluation. Based on information provided in this NDA submission, the clinical pharmacology review team concluded that changing the assay laboratory was not an issue and that the plasma T data from the new laboratory was acceptable.

While the new laboratory was re-assaying the ongoing subjects' stored Visit 2 blood samples, subjects continued taking their current study product dose until new re-assay values were available to re-evaluate their titration outcome. Subjects were considered to have "restarted" the study based on the Visit 2 blood sample new re-assay results and were evaluated for a titration decision at their new "Visit 3". The Applicant submitted protocol Amendment 2 (dated 6-30-2016) on July 14, 2016 under IND 78104, supporting document number 096 to describe this study conduct change and redefined subject clinical visits as Visit 3b, Visit 4b, and Visit 5b in protocol Amendment 3 (dated 3-6-2017) submitted on March 24, 2017 under IND 78104 supporting document 107. No subjects had reached the initial Visit 6 at the time of the laboratory change, so all clinical visits after Visit 5b were termed as Visit 6 and Visit 7 (endpoint). Visit 7 is termed as "study end" in this review because all subjects no longer had the initial end of study time point of 105 days.

3.2 Evaluation of Efficacy

The Applicant has submitted one pivotal clinical study (CLAR-15012) designed to demonstrate the efficacy and safety of oral TU capsules for the treatment of adult male hypogonadism. This review will focus on the primary endpoint of proportion of men who achieve a normal plasma total testosterone level.

3.2.1 Study CLAR-15012 Design and Endpoints

Study CLAR-15012 was initially planned to be a 4-month (105-day), open-label, repeat dose, dose-titration, multicenter, Phase 3 study in 135 hypogonadal men. Eligible subjects were adult men 18 to 65 years of age with a clinical diagnosis of hypogonadism and who had two morning serum total testosterone levels less than 300 ng/dL at screening over two separate days. Subjects were also to have been naïve to androgen replacement therapy or adequately washed out of prior androgen replacement therapies and remain off them.

All subjects began at a dose of 237 mg TU twice daily (BID) and could be titrated up to 396 mg TU BID. Subjects were to take their study medication immediately prior to breakfast and dinner. Dose-titration occurred on Visit 3 (Visit 3b) and Visit 5 (Visit 5b), if needed, based on the plasma T concentration (C_{avg}) derived from the 24-hour serial sample drawn on Visit 2 and Visit 4 (Visit 4b). Baseline plasma total testosterone level was measured as the mean of two morning samples collected one hour apart prior to first study drug dose.

Oral TU is available as three dosage strengths: 158 mg TU, 198 mg TU, and 237 mg TU. The titrated dose ranged from 158 mg BID to 396 mg BID and was taken as one of the following:

one 158 mg TU capsule, BID	two 158 TU mg capsules, BID (equal to 316 mg BID)
one 198 mg TU capsule, BID	two 198 mg TU capsules, BID (equal to 396 mg BID)
two 237 mg TU capsules, BID	

Primary Efficacy Endpoint

The primary objective was to determine the efficacy of oral TU in hypogonadal men based on the percentage of treated subjects that had a 24-hr average plasma testosterone concentration (C_{avg}) in the normal range (≥ 252 ng/dL and ≤ 907 ng/dL). Because the duration of exposure to study drug was extended due to the change in

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assay laboratory, the number of treatment days was greater than the originally planned 105 days. Therefore, the study endpoint occurred at the subject's last study visit (Visit 7) and designated as "study end" in this review.

The primary efficacy variable was the percentage of treated subjects with a plasma total T C_{avg} within the normal range at study end (Visit 7), with success being defined as at least 75% of subjects are within the normal range (≥ 252 ng/dL and ≤ 907 ng/dL) and with a lower bound of the 95% confidence interval of at least 65%.

3.2.2 Statistical Methodologies

Primary Efficacy Endpoint

The primary efficacy analysis is the percentage of subjects who attain a plasma total T C_{avg} value within the normal range at end of study (Visit 7) in the modified ITT (MITT) population, defined as all randomized subjects who took at least 1 dose of study drug. This percentage is summarized descriptively and the 95% confidence interval is approximated by a binomial distribution.

To account for missing data, the following rules were applied if any of the listed events occurred:

- A subject was defined as a failure if they: 1) died before Visit 7, 2) experienced an adverse event that led to stopping oral TU, or 3) did not tolerate TU or reported it was not effective.
- A last observed value was imputed for the missing Visit 7 value if a subject: 1) moved from area, 2) withdrew consent without indicating that it was related to the therapy, 3) was lost to follow-up, or 4) did not have a measurement on Visit 7.

Sample Size

A total of 135 subjects were initially randomized to oral TU so that 120 subjects complete through Visit 7. This total is based on the following assumptions: 2-sided one-sample binomial test at 5% significance level, at least 90% power, 86% success rate (based on modeling of Phase 3 pharmacokinetic data), 75% minimum success threshold, and 12% drop-out rate.

The final number of subjects randomized to oral TU increased from 135 to 166. The clinical study report states on page 78 that, "Due to the lower than predicted screen failure rate, and the higher than anticipated pace of screening, enrollment in the study exceeded the original sample size identified in the original protocol."

3.2.3 Study CLAR-15012 Subject Disposition and Baseline Characteristics

Table 3.1 presents the number of subjects and their disposition for study CLAR-15012. A total of 166 oral TU subjects were enrolled and all took study product at 31 centers in the U.S. The overall discontinuation rate was 7.2% (12 subjects). Reasons for premature study discontinuation in these 12 subjects included subject request (3.0% or 5 subjects), adverse event (2.4% or 4 subjects), lost to follow-up (1.2% or 2 subjects), and noncompliance with study drug (0.6% or 1 subject1).

Table 3.1
Study CLAR-15012: Enrollment and Disposition of Subjects

	Oral TU
Number of Enrolled	166
Number Who Took Study Product (Safety/Efficacy Population)	166
Completed n (%)	154 (92.8)
Discontinued n (%)	12 (7.2)
Primary Reason for Discontinuation n (%):	
Subject Request	5 (3.0)
Adverse Event	4 (2.4)
Lost to Follow-Up	2 (1.2)
Non-Compliance with Study Drug	1 (0.6)

Source: Table 9, page 83, Study CLAR-15012 report and Statistical Reviewer's listing.

The majority of subjects was Caucasian (80.1%). Overall, subjects had a mean age of 51.6 years and a mean screening serum total testosterone concentration of 192.6 ng/dL. The type of hypogonadism is distributed as follows: 75 subjects (45.2%) had primary, 28 subjects (16.9%) had secondary, 3 subjects (1.8%) had combined/undefined, and 60 subjects (36.1%) had unknown type.

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Of the 166 subjects who took study drug, 15 (9.0%) did not have plasma T C_{avg} data at Visit 7. Of these 15 subjects, 12 (7.2%) discontinued study prior to Visit 7 and 3 (1.8%) did not have sufficient pharmacokinetic data at Visit 7 to calculate plasma T C_{avg} at Visit 7. All 15 subjects had post-baseline plasma T C_{avg} data.

3.2.4 Study CLAR-15012 Results and Conclusions

Primary Efficacy Endpoint

This reviewer has verified the Applicant's primary efficacy results based on the percentage of subjects with a plasma total testosterone C_{avg} in the normal range at study end in the efficacy population. Efficacy was demonstrated; the percentage of subjects with a plasma total T C_{avg} level within the normal range at study end was 87.3% (145 of 166 subjects) with 95% confidence interval (CI) of 81.3% to 92.0%.

Assuming a worst-case scenario where a subject is considered a failure if they did not have a Visit 7 C_{avg} value, the endpoint percentage is 83.1% (138/166) with 95% CI of 76.6% to 88.5%; which also meets both criteria.

3.3 Evaluation of Safety

For information about the evaluation of safety, refer to the clinical evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

No subgroup analyses by gender or geographic region were necessary because all subjects were men and the study was conducted in the United States. There were too few non-Caucasian subjects (< 20%) and no subjects greater than 65 years to conclude if the efficacy endpoint was similar by race or age group. No other subgroups of interest with respect to efficacy were identified by the clinical reviewer.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

No statistical issues were identified in this submission.

5.2 Collective Evidence

The one submitted study provides evidence demonstrating the efficacy of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism based on the proportion of men who achieved total plasma testosterone levels within the normal range, defined as ≥ 252 ng/dL and ≤ 907 ng/dL, at study end (Visit 7) in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the proportion of men achieving the total plasma testosterone levels within the normal range no less than 65%. The percentage of men with a plasma total T C_{avg} level within the normal range at study end was 87.3% (145 of 166 subjects) with 95% confidence interval of 83.1% to 92.0%.

5.2 Conclusions and Recommendations

The one submitted study provides evidence demonstrating the efficacy of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism.

Reference ID: 4221052

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SONIA CASTILLO
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02/13/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number:	NDA 206089
Drug Name:	Testosterone Undecanoate
Indication(s):	Replacement therapy (TRT) in males for condition associated with a deficiency of endogenous testosterone : • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Studies	Six-Month Oral Gavage Carcinogenicity Study in Male CByB6F1-Tg(HRAS)2Jic (tg/wt) Mice
Applicant:	Clarus Therapeutics Inc 555 Skokie Blvd., Suite 340 Northbrook, IL 60062 Test Facility (b) (4)
Documents Reviewed:	Electronic submission: Submitted on July 12, 2017 Electronic data: Submitted on July 12, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -VI
Statistical Reviewer:	Malick Mbodj, Ph.D.
Secondary Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Reproductive and Urologic Products
Reviewing Pharmacologist:	Yangmee Shin, Ph.D.
Project Manager:	Jeannie Roule
Keywords:	Carcinogenicity, Dose response

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1. Background

In this submission the sponsor included a carcinogenicity study report in transgenic mice. This study was intended to assess the carcinogenic potential of testosterone undecanoate in male mice when administered orally by gavage at appropriate drug levels for about 26 weeks. All mice in Groups 0-3 were terminally sacrificed in Week 27. The positive control group was scheduled for early terminal sacrifice at Week 23. Results of this review have been discussed with the reviewing pharmacologist Dr. Shin.

In this review the phrase "dose response relationship"(trend) refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Mouse Study

One hundred and fifteen Tg rasH2 transgenic male mice were assigned randomly to one of the five groups which included three treated groups, one vehicle control group and one positive control group in equal size of 25 animals except the positive control group which had 15 animals. The dose levels for treated groups were 20, 40, and 80 mg/kg/day, as indicated in Table 1. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (0.5% w/v CMC and 0.1% w/v polysorbate 80 in deionized water) administered orally by gavage for about 26 weeks in the same manner as the treated groups. The positive control was administered with a single IP injection of MNU (methylnitrosourea) at 75 mg/kg. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. Spontaneous deaths were noted in the positive control mice resulting in early termination of this group at Week 23.

Table 1: Experimental Design in Mouse Study

Group Name	Group N0.	Dose Level (mg/kg/day)	Number of Animal Males
Vehicle Control	0	0	25
Low	1	20	25
Medium	2	40	25
High	3	80	25
Positive control	4	75	15

The positive control was administered with a single IP injection of MNU.
All animals were euthanized during week 27, (Groups 0-3) or week 23 (Groups 4)

During the study period, all animals were observed for general health/mortality and moribundity twice daily on weekdays (at least four hours apart, once in the morning and once in the afternoon) and at least once on weekends and holidays, throughout the study. During the first week of administration, cage-side observations were performed approximately 1-2 hours after dose administration; each animal was removed from the cage and observed in detail on the day of randomization, and weekly during the dosing period. Any animal showing signs of severe debility or intoxication, and if determined to be moribund or suffering excessively will be euthanized. Observations will include, but will not be limited to, evaluation for reaction to treatment. Histopathological examinations were performed on all animals found dead or killed moribund or sacrificed at the end of the experiment. Body weights of individual animals were obtained on the day of randomization and weekly thereafter. Animals showing weight loss or deterioration in condition will be weighed more frequently as necessary.

2.1. Sponsor's analyses

2.1.1. Survival analysis

No detail of their survival analysis method was specified in their report.

Sponsor's findings:

The sponsor's report concluded that, survival was unaffected in the testosterone undecanoate -treated mice; early deaths were confined to a single mouse/ testosterone undecanoate -treated or vehicle control group (1/25).

2.1.2. Tumor data analysis

Statistical analysis for tumor data was not performed due to low incidence of tumors in vehicle control and high dose groups.

Adjustment for the multiplicity:

No detail of their adjustment method was specified in their report.

Sponsor's findings:

The sponsor's report concluded that, the testosterone undecanoate does not have carcinogenic activity or potential when administered daily for 26 weeks via oral gavage at doses up to 80mg/kg/day.

2.2 Reviewer's analyses

This reviewer independently performed the survival data analyses, tumor data analyses and additional analyses suggested by the reviewing pharmacologist. Data used in this reviewer's analyses were provided by the sponsor electronically on July 12, 2017 via SN032.

2.2.1 Survival analysis

In the reviewer's analysis, intercurrent mortality data were analyzed using the Kaplan-Meier product limit method. The Kaplan-Meier's curve was presented graphically. The dose response relationship and homogeneity of survival distributions were tested for the treatment groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 1A in the appendix. The Kaplan-Meier curve for survival rate is given in Figures 1A in the appendix. Results of the tests for dose response relationship and homogeneity of survivals are given in Tables 2A in the appendix.

Reviewer's findings:

This reviewer's analysis showed the numbers of male mice surviving to their terminal necropsy were 24, 24, 24, 24, and 8, in vehicle control, low, medium, high, and positive control groups. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group.

This reviewer's analysis showed the positive control group had a statistically significant increase in unscheduled death compared to the vehicle control group, (p<0.0001)

2.2.2. Tumor data analysis

In the reviewer's analysis, the tumor data were analyzed for dose response relationship across vehicle control group and the treated groups, as well as the pairwise comparisons of vehicle control group with each of the treated groups using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice with development of the tumor type being tested gets a score of s_h =1. An animal that dies at Week w_h without development of the given tumor type before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h . As an interpretation, an animal with score s_h =1 can be considered as a whole animal, while an animal with score s_h <1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal develops the given tumor being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise comparison) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature [Gebregziabher and Hoel (2009), Moon et al. (2003), Portier, et al. (1986)]. Hence, this reviewer used k=3 for the analysis of the data. Based on the intent to treat (ITT) principle Wmax was considered as 27.

For the calculation of p-values, if there were less than 10 tumor bearing animals across all treatment groups for a given tumor type, the exact tests based on the discrete permutation distribution were used, with dose levels (0, 20, 40, and 80) as scores, and asymptotic tests were used for tumor types with higher incidences. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A in the appendix for male mice.

Multiple testing adjustments:

Following FDA 2001 draft guidance for the carcinogenicity study design and data analysis, for mouse study the significance levels were 0.05 for all dose response relationship tests and pairwise comparisons, regardless of common or rare tumors.

Reviewer's findings:

Following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased testosterone undecanoate dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in testosterone undecanoate treated groups, when compare to the vehicle control group.

The pairwise comparisons showed statistically significant increases in the positive dose group for the incidences of lymphoma in adrenal, heart, kidney, liver, lymph nodes (mandibular and mesenteric), spleen, and thymus, and papilloma in stomach were statistically significant higher in the positive control

when compared to the vehicle control group in male mice (p-values =0.0140, 0.0040, 0.0040, 0.0040, 0.0183, 0.0008, <0.000, <0.000, <0.000, respectively), as indicated in Table 4A.

3. Summary

In this submission the sponsor included a carcinogenicity study report in transgenic mice. This study was intended to assess the carcinogenic potential of testosterone undecanoate in male mice when administered orally by gavage at appropriate drug levels for about 26 weeks. All mice in Groups 0-3 were terminally sacrificed in Week 27. The positive control group was scheduled for early terminal sacrifice at Week 23.

One hundred and fifteen Tg rasH2 transgenic male mice were assigned randomly to one of the five groups which included three treated groups, one vehicle control group and one positive control group in equal size of 25 animals except the positive control group which had 15 animals. The dose levels for treated groups were 20, 40, and 80 mg/kg/day, as indicated in Table 1. In this review these dose groups would be referred to as the low, medium, and high dose group, respectively. The vehicle control group received the vehicle (0.5% w/v CMC and 0.1% w/v polysorbate 80 in deionized water) administered orally by gavage for about 26 weeks in the same manner as the treated groups. The positive control was administered with a single IP injection of MNU (methylnitrosourea) at 75 mg/kg. This group was included to verify sensitivity of the test system to detect carcinogenicity effect. Spontaneous deaths were noted in the positive control mice resulting in early termination of this group at Week 23.

This reviewer's analysis showed the numbers of male mice surviving to their terminal necropsy were 24, 24, 24, 24, and 8, in vehicle control, low, medium, high, and positive control groups. This reviewer's analysis showed no statistically significant increase in mortality across the vehicle control group and the three treated groups. The pairwise comparisons showed no statistically significant increase or decrease in mortality between the treated groups, and the vehicle control group.

This reviewer's analysis showed the positive control group had a statistically significant increase in unscheduled death compared to the vehicle control group, ($p<0.0001$)

For tumor data, following the multiple testing adjustment method described above, this reviewer's analyses showed no tumor types with a statistically significant dose response relationship in tumor incidences with increased testosterone undecanoate dose. The pairwise comparisons also showed no tumor types with a statistically significant increase in tumor incidences in testosterone undecanoate treated groups, when compare to the vehicle control group.

The pairwise comparisons showed statistically significant increases in the positive dose group for the incidences of lymphoma in adrenal, heart, kidney, liver, lymph nodes (mandibular and mesenteric), spleen, and thymus, and papilloma in stomach were statistically significant higher in the positive control when compared to the vehicle control group in male mice (p-values =0.0140, 0.0040, 0.0040, 0.0040, 0.0183, 0.0008, <0.000, <0.000, <0.000, respectively), as indicated in Table 4A.

Malick Mbodj, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D. Team Leader, DBVI
Hepei Chen, secondary reviewer

cc:
Archival NDA 206089- testosterone undecanoate
Dr. Tsong Ms. Patrician Dr. Lin
Dr. Shin Jeannie Roule

4. Appendix

Table1A: Intercurrent Mortality Rate
Male Mice

	0mg|kg|day Vehicle Cont.		**20mg|kg|day**		**40mg|kg|day**		**80mg|kg|day**		**75 mg|kg|day Positive Cont.**	
Week	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**	**No. of Death**	**Cum. %**
0 - 13	.	.	.	.	.	.	.	.	.	.
14 - 27	1	4.00	1	4.00	1	4.00	1	4.00	7	46.67
Ter. Sac.	24	96.00	24	96.00	24	96.00	24	96.00	8	53.33
Total	25	100.00	25	100.00	25	100.00	25	100.00	15	100.00

Table 2A: Intercurrent Mortality Comparison for
Male Mice

Test Statistics	**P-value for Vehicle Cont. Low, Med, high**	**P-value for Vehicle Cont. vs Low**	**P-value for Vehicle Cont. vs Med**	**P-value for Vehicle Cont. vs High**	**P-value for Vehicle Cont. vs Positive Cont.**
Dose-Response (Likelihood Ratio)	0.9951	1.0000	0.9885	0.9885	<.0001*
Homogeneity (Log-Rank)	1.0000	1.0000	0.9885	0.9885	0.0001*

* = statistically significant at the 0.05 significance level.

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and The pairwise Comparisons

Male Mice Using Poly-3 test

Organ Name	Tumor Name	0 mg untr Cont N=25	20 mg place cont N=25	40 mg Low N=25	80 mg Med N=25	75 mg High N=15	P_Value Dose Resp	P_Value VCvs.L	P_Value VCvs.M	P_Value VCvs.H	P_Value VCvs.PC
Adrenal	Lymphoma	0	0	0	0	3	.	.	.	.	0.0140*
Diaphragm	Carcinoma	0	0	0	0	1	.	.	.	.	0.2647
Epididymides	Carcinoma	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	1.0000
Heart	Lymphoma	0	0	0	0	4	.	.	.	.	0.0040*
Kidney	Lymphoma	0	0	0	0	4	.	.	.	.	0.0040*
Liver	Lymphoma	0	0	0	0	4	.	.	.	.	0.0040*
Lung	Adenoma	0	0	0	1	0	0.2525	.	.	0.5000	.
	Lymphoma	0	0	0	0	1	.	.	.	.	0.2647
Lymph Node Mandibular	Lymphoma	0	0	0	0	3	.	.	.	.	0.0183*
Lymph Node Mesenteric	Lymphoma	0	0	0	0	5	.	.	.	.	0.0008*
Pancreas	Carcinoma	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	1.0000
Salivary Gla	Lymphoma	0	0	0	0	1	.	.	.	.	0.2647
Skin	Carcinoma	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	1.0000
Small Intest	Carcinoma	0	0	0	0	1	.	.	.	.	0.2647
Spleen	Fibroma	1	0	0	0	0	1.0000	1.0000	1.0000	1.0000	1.0000
	Lymphoma	0	0	1	0	9	0.5000	.	0.5000	.	<0.000*
Stomach	Carcinoma	1	0	0	1	1	0.5001	1.0000	1.0000	0.7551	0.4652
	Papilloma	0	0	0	0	11	.	.	.	.	<0.000*
Tail	Papilloma	2	0	0	0	0	1.0000	1.0000	1.0000	1.0000	1.0000
Thymus	Lymphoma	0	0	0	0	8	.	.	.	.	<0.000*
Thyroid	Lymphoma	0	0	0	0	1	.	.	.	.	0.2647

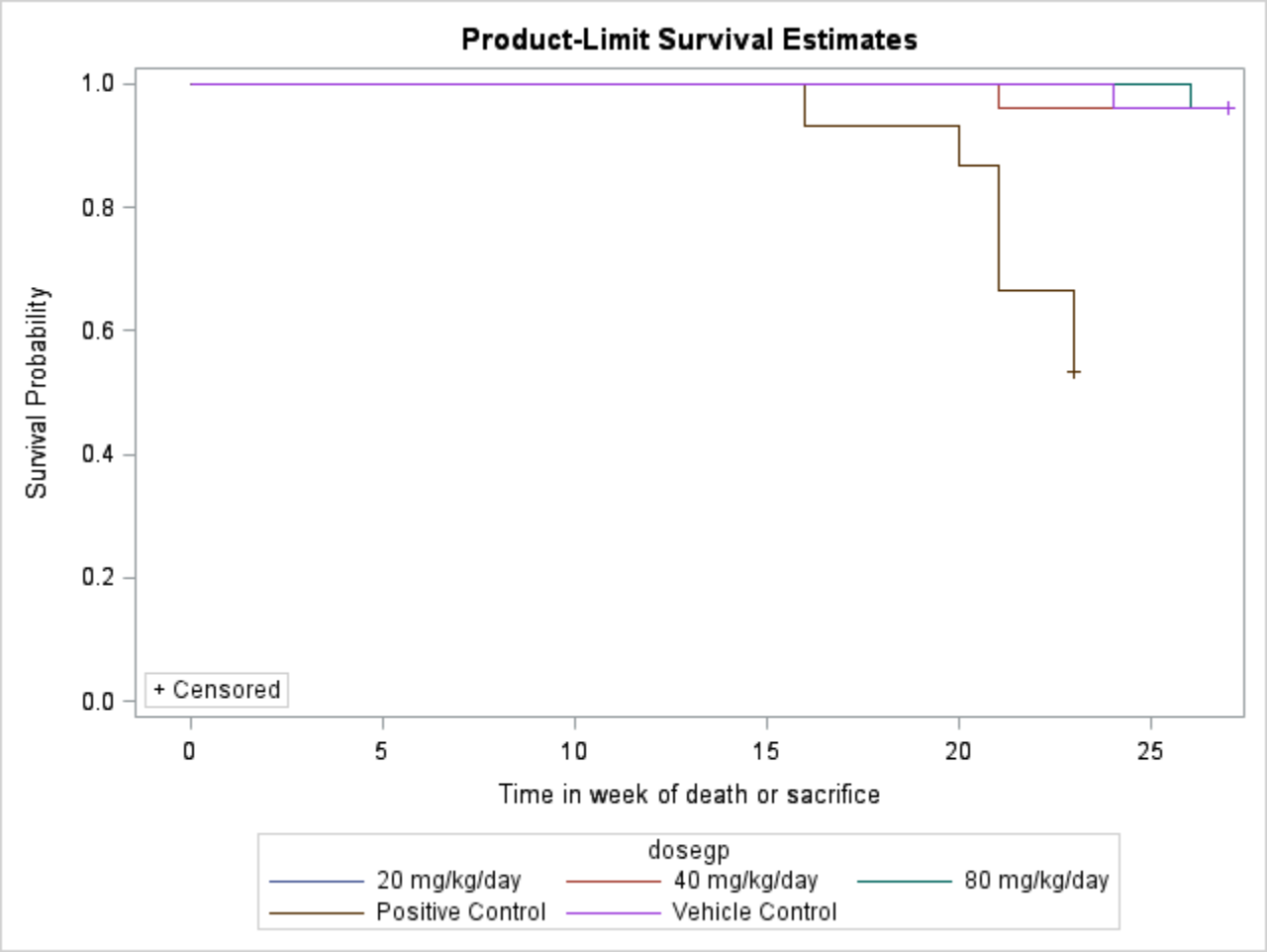
Table 4A: Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or the pairwise Comparisons

Positive control Group and Vehicle Control Group for Mice

Organ Name	Tumor Name	0 mg Vehicle Control N=25	75 mg positive Control N=15	P_Value Vehicle Control vs. Positive Control
Adrenal	Lymphoma	0	3	0.0140*
Heart	Lymphoma	0	4	0.0040*
Kidney	Lymphoma	0	4	0.0040*
Liver	Lymphoma	0	4	0.0040*
Lymph Node Mandibular	Lymphoma	0	3	0.0183*
Lymph Node Mesenteric	Lymphoma	0	5	0.0008*
Spleen	Lymphoma	0	9	<0.000*
Stomach	Papilloma	0	11	<0.000*
Thymus	Lymphoma	0	8	<0.000*

* = statistically significant at the 0.05 significance level.

Figure 1A: Kaplan-Meier Survival Curves for
Male Mice



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/s/

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Concur with review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
Clinical Studies

NDA/Supporting Doc. #:	206089 / 001
Drug Name:	Oral Testosterone Undecanoate
Indication(s):	Treatment of adult male hypogonadism
Applicant:	Clarus Therapeutics, Inc.
Date(s):	Letter Date: January 3, 2014 PDUFA Date: November 3, 2014
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Bone, Reproductive, and Urologic Products
Clinical Team:	Jin Chen, M.D., Clinical Reviewer Mark Hirsch, M.D., Clinical Team Leader
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Key Words: Clinical studies, NDA review

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APPENDIX 10

Reference ID: 3638702

1. EXECUTIVE SUMMARY

The one submitted study does not provide evidence demonstrating the efficacy of testosterone undecanoate capsules for the treatment of adult male hypogonadism based on the proportion of men who achieved total serum testosterone levels within the normal range. This conclusion was based on the totality of both the pre-specified and post hoc sensitivity analyses after addressing the impact of a high percentage of missing values. The primary efficacy outcome, the proportion of men with normal total serum testosterone levels was not within the pre-specified success criteria for the product. The men who received the product after possible dose titration did not achieve the pre-specified success criteria for proportions of men with normal total serum testosterone levels.

The evidence is based on achieving total serum testosterone levels within the normal range after 90 days of treatment in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the proportion of men achieving the total serum testosterone levels within the normal range no less than 65%. The normal range of total serum testosterone level is defined as ≥ 300 ng/dL and ≤ 1000 ng/dL.

The pre-specified primary efficacy analysis was based on the completer population that did not include 19.4% of subjects who took study drug but did not have a serum total testosterone data at the time point of interest. To address the issue of missing data, which appeared to be non-random, various post hoc sensitivity analyses were conducted by this reviewer and the Applicant to assess the impact of missing data on the consistency of the efficacy results. Although the pre-specified analysis in the completer population achieved success, none of the post hoc sensitivity analyses achieved success. Therefore, from a statistical perspective, the evidence of efficacy from this submitted study is not robust.

2. INTRODUCTION

2.1 Overview

This submission consists of one open-label, single-arm, multicenter, dose titration study to evaluate the efficacy and safety of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism. Table 2.1 presents a brief study summary.

Table 2.1
Brief Summary of Clinical Study for Testosterone Undecanoate (TU)

Study Number (Country / #) Dates of Study Conduct	Subject Population	Treatment	ITT[1] Population	Design[2]
CLAR-12011 (United States / 24) Feb 2013 to July 2013	Men aged 18 to 75 years with clinically verified hypogonadism (total serum testosterone levels < 300 ng/dL)	200 to 600 mg of T daily **Total**	144 **144**	OL,SA, DT, MC, 114 days

Source: Statistical Reviewer's listing.
[1] ITT = Intent to Treat, received investigational product
[2] OL = Open-label, SA = Single Arm, DT = Dose Titration, MC = Multicenter

The proposed indication is:

Testosterone undecanoate capsules are indicated for the treatment of adult male hypogonadism.

The proposed dose of testosterone undecanoate is 100 mg to 300 mg of testosterone twice daily.

Testosterone replacement is used to treat the symptoms of hypogonadism and according to the Applicant:

> Testosterone (T) is the primary androgenic hormone produced in the interstitial cells of the testes. The physiologic actions of serum T are mediated by free (unbound) T or by dihydrotestosterone (DHT), the 5α-reduced metabolite of T. The physiologic actions are mediated via interaction with intracellular androgen receptors, which bind both T and DHT. Androgens are responsible for the normal growth, development, and maintenance of the male sex organ, function of the testes, prostate, and seminal vesicle, and secondary sex characteristics (deepening voice, muscular development, facial hair, etc.).
>
> Male hypogonadism, or Androgen Deficiency Syndrome, is diagnosed when unequivocally low serum T levels, typically less than 300 ng/dL, and consistent symptoms and signs are present in a man. The signs and symptoms consistent with hypogonadism include reduced sexual desire (libido) and activity, decreased spontaneous erections, breast discomfort, gynecomastia, loss of body hair, low bone mineral density, hot

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flushes, decreased energy or motivation, depressed mood, poor concentration or memory, mild anemia, reduced muscle bulk and strength, and increased body fat. Hypogonadism is also associated with the development of the metabolic syndrome and increased risk of coronary artery disease.

Testosterone replacement therapy (TRT) has been used for decades to treat male hypogonadism. (*Source: Clinical Study Report CLAR-12011, section 7, page 11*)

The study is designed to demonstrate the efficacy of testosterone undecanoate for the treatment of adult male hypogonadism.

2.2 Data Sources

The application was submitted electronically. The submitted SAS data sets were complete and well documented. The following review items are located in the CDER Electronic Document Room as described below:

- The complete study report was submitted three times under submission dates 1-2-2014 (eCTD Sequence Number 0000), 2-28-2014 (eCTD Sequence Number 0004), 3-28-2014 (eCTD Sequence Number 0005) with the last submission containing the most up-to-date version which is located at \\CDSESUB1\evsprod\NDA206089\0005\m5\53-clin-stud-rep\535-rep-effic-safety-stud\male-hypogonadism\5351-stud-rep-contr\clar-12011-csr and responses to information requests are located at \\Cdsesub1\evsprod\NDA206089\0009 , \\Cdsesub1\evsprod\NDA206089\0011 , \\Cdsesub1\evsprod\NDA206089\0014 , and \\Cdsesub1\evsprod\NDA206089\0016 under submission dates 5-2-2014 (eCTD Sequence Number 0009), 7-17-2014 (eCTD Sequence Number 0011), 8-4-2014 (eCTD Sequence Number 0014), and 8-12-2014 (eCTD Sequence Number 0016), respectively.
- Raw and derived data sets used for analysis and the data set define and program files are located at \\CDSESUB1\evsprod\NDA206089\0000\m5\datasets\clar-12011-csr under submission date 1-2-2014 (eCTD Sequence Number 0000)

3. STATISTICAL EVALUATION

This section describes the study design, data and analysis quality, evaluation of efficacy, and study results.

3.1 Data and Analysis Quality

The submitted datasets were well documented and easily accessible. The derived efficacy datasets used for the primary efficacy analysis can be created from the raw datasets. I was able to reproduce the primary efficacy results as presented in the study report from the derived efficacy dataset based on frequency of events. The final statistical analysis plan was submitted prior to unblinding and there were no changes to the pre-specified primary analyses as presented in the protocol.

There was one issue identified that affected the quality of the analysis. The pre-specified primary efficacy analysis was based on the completer population that did not include 19.4% of subjects who took study drug but did not have endpoint data. The primary efficacy analysis should be conducted in all subjects who took study drug, that is, the intent-to-treat population. In addition, the protocol did not address how missing data would be accounted for in the primary efficacy analysis. The combination of a large percentage of missing data (19.4%) and an inappropriate primary efficacy population contributed to this lack of accountability.

To address this issue, this reviewer conducted two post hoc sensitivity analyses in all subjects who received at least one dose of study drug to assess the impact of missing data on the consistency of the efficacy results. The Applicant also submitted five additional sensitivity analyses in different analysis populations and based on different methodologies in response to the Agency's request to account for the missing data. Sensitivity analyses are important for this product because of the extent of missing data (19.4%) and because the pre-specified primary analysis result in the completer population is exactly the threshold value used to demonstrate efficacy, which needs to be re-evaluated to determine how it is affected by the missing data.

3.2 Evaluation of Efficacy

The Applicant has submitted one pivotal clinical study (CLAR-12011) designed to demonstrate the efficacy and safety of oral TU capsules for the treatment of adult male hypogonadism. This review will focus on the primary endpoint of proportion of men who achieve a normal total serum testosterone level.

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3.2.1 Study CLAR-12011 Design and Endpoints

Study CLAR-12011 was a 4-month (114-day), open-label, repeat dose, dose-titration, multicenter, Phase 3 study in hypogonadal men. Eligible subjects were adult men 18 to 75 years of age with a diagnosis of hypogonadism who had morning serum total testosterone level < 300 ng/dL at screening. Subjects were also to have been naïve to androgen replacement therapy or adequately washed out of prior androgen replacement therapies and remain off them. About 120 subjects were planned to be enrolled.

All subjects began at an oral dose of 200 mg T, twice daily (BID) and could be titrated up to 300 mg T, BID. Subjects were instructed to take their study medication with food. Dose-titration occurred on days 42 and/or 84, if needed, based on the serum T concentration derived from the sample drawn on day 30 and day 72. The titrated dose could be up to 300 mg T BID.

Serum total testosterone level was measured as: 1) the mean of two samples collected one hour apart between 6:00 and 10:00 AM at screening and at baseline (prior to first study drug dose), 2) the 12-hour (post morning dose) serial sampling average concentration (C_{avg}) on days 30 and 72, and 3) the 24-hour (12 hours post morning dose and 12 hours post evening dose) serial sampling C_{avg} on day 114.

Oral TU capsules are available as two dosage forms: 100 mg testosterone (as 158.3 mg oral TU) or 150 mg testosterone (as 237.5 mg oral TU). The initial dose was 200 mg (two T 100 mg capsules) BID. The titrated dose was one doses listed below. Bottles containing 120 capsules each were distributed at study visits.

one T 100 mg capsule, BID	one T 100 mg capsule and one T 150 mg capsule, BID
one T 150 mg capsule, BID	two T 150 mg capsules, BID
two T 100 mg capsules, BID	

Primary Efficacy Endpoint

The primary objective was to determine the efficacy of oral TU in hypogonadal men based on the percentage of treated subjects that had a 24-hr average serum testosterone concentration (C_{avg}) in the normal range (≥ 300 ng/dL and ≤ 1000 ng/dL) after 114 days of therapy.

The primary efficacy variable was the percentage of treated subjects with a serum total T C_{avg} value within the normal range on day 114, with success being defined as at least 75% of treated subjects are within the normal range (≥ 300 ng/dL and ≤ 1000 ng/dL) and with a lower bound the of 95% confidence interval of at least 65%.

3.2.2 Statistical Methodologies

The final version of the protocol, dated December 17, 2012 and submitted on January 4, 2013 under supporting document number 59, did not specify the primary efficacy population or how missing data would be accounted for in the primary efficacy analysis. The statistical analysis plan (SAP), finalized on August 7, 2013, was not submitted to the FDA for review but was included in the NDA submission. The SAP is the first place and time that any mention of the primary efficacy population and other analysis populations but the handling of missing data for the primary analysis is not addressed.

The statistical analysis plan specified the following three populations for efficacy analysis:

- The efficacy population, defined as all subjects who completed the day 114 visit with sufficient pharmacokinetic data to calculate serum T C_{avg}, is the <u>primary efficacy population</u>. This can also be described as the completer population.
- The safety analysis population is defined as all subjects who receive at least one dose of the study drug.
- The pharmacokinetic (PK) population is defined as all subjects who have sufficient data points to calculate at least one PK parameter.

This reviewer does not agree with the designation of the efficacy population as the primary efficacy population. Instead, the primary efficacy population should be the safety population because it includes all subjects who received at least one dose of study drug. In this study, basing the primary efficacy analysis on the efficacy

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population resulted in the exclusion from the analysis of 19.4% of subjects who took study drug because they did not have day 114 serum T C_{avg} values. This amount of missing data is large for a study that is short term (4 months), open-label, and single-arm for a product that is indicated for chronic use. Also, reducing the number of subjects included in the denominator by 20% when calculating a percentage biases the value towards a more favorable result.

This reviewer conducted two post hoc sensitivity analyses using the safety population to assess the impact of missing data on the consistency of the efficacy results. The Applicant also submitted five additional sensitivity analyses in different analysis populations and based on different methodologies in response to the Agency's request to account for the missing data. One of these analyses used the PK population but this analysis set still excludes 7.6% of subjects who took study drug (range of 4 to 60 days) but did not have any post-baseline serum T C_{avg} values. Sensitivity analyses are important for this product because of the extent of missing data (19.4%) and because the pre-specified primary analysis result in the completer population is exactly the threshold value used to demonstrate efficacy, which needs to be re-evaluated to determine how it is affected by the missing data.

Primary Efficacy Endpoint

The pre-specified primary efficacy analysis is the percentage of subjects who attain a serum total T C_{avg} value within the normal range at day 114 in the efficacy population. This percentage is summarized descriptively and the 95% confidence interval is approximated by a binomial distribution.

Table 3.1 presents the post hoc sensitivity analyses conducted by both this reviewer and the Applicant to account for the large amount of missing day 114 data for serum total T C_{avg}.

Table 3.1
Study CLAR-12011: Post Hoc Sensitivity Analyses Conducted by the Statistical Reviewer and the Applicant to Assess the Impact of Missing Data on the Efficacy Results

	Analysis Assumptions and Population Used
Statistical Reviewer's Post Hoc Analyses	
Last Observation Carried Forward (LOCF)	Carried forward the last available serum total T C_{avg} value (baseline, day 30, or day 72) during the treatment period and used the *safety population*
Worst Case	Assumed that the missing day 114 serum total T C_{avg} value was outside the normal range and used the *safety population*
Sponsor Post Hoc Analyses	
LOCF	Carried forward the last available serum total T C_{avg} value (baseline, day 30, or day 72) and used the *pharmacokinetic population*
Worst Case	Assumed that the missing day 114 serum total T C_{avg} value was outside the normal range and used the *pharmacokinetic population*
Mixed Model Repeated Measures (MMRM) with Multiple Imputation	Model included available day 30 and day 72 data , 50 imputations conducted, and used the *pharmacokinetic population*
MMRM with Multiple Imputation with demographics	Model included available day 30 and day 72 data, diabetes screening status (Y/N) and smoking history (never/former/current) , 50 imputations conducted, four subjects who dropped out due to tolerability or key adverse events were classified as having their serum T C_{avg} value out of range, and used the *safety population*

Source: Statistical Reviewer's listing.

Rationale for Using LOCF

This statistical reviewer's rationale for using LOCF and worst case scenario analyses are as follow:

- Worst case scenario gives an idea of the smallest point estimate of efficacy in this study
- Per the clinical reviewer, a subject's T level should rise and reach a steady state level after a few days of correctly taking the study drug with normal T levels achieved after continued use. Conversely, if no study drug is taken, the subject's T level will remain low. In these 28 subjects who took study drug but did not have day 114 data, 17

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subjects have values on either day 30 or day 72 and 11 subjects did not have any post-baseline values. The T values for these subjects are presented in Table A.2 in the Appendix.

Sample Size

A total of 120 subjects were enrolled so that 90 subjects complete through day 114. This total is based on the following assumptions: 2-sided one-sample binomial test at 5% significance level, 85% power, 86% success rate (based on Phase 2 study result), 75% minimum success threshold, and 25% drop-out rate.

3.2.3 Study CLAR-12011 Subject Disposition and Baseline Characteristics

Table 3.2 presents the number of subjects and their disposition for study CLAR-12011. A total of 148 subjects were enrolled, of which 144 took study product at 24 centers in the U.S. The overall discontinuation rate was 18.8% (27 subjects). Reasons for premature discontinuation from study in these 27 subjects included withdrawal of consent (5.6% or 8 subjects), lost to follow-up (3.5% or 5 subjects), other (3.5% or 5 subjects), adverse event (2.1% or 3 subjects), hematocrit greater than 54% (2.1% or 3 subjects), noncompliance with study drug (1.4% or 2 subjects), and protocol violation (0.7% or 1 subject).

Table 3.2
Study CLAR-12011: Randomization and Disposition of Subjects

	Oral TU
Number of Enrolled	148
Number Who Took Study Product (Safety Population)	144
Completed n (%)*	117 (81.2)
Discontinued n (%)*	27 (18.8)
Number in the Pharmacokinetic Population	133 (92.4)
Number in the Efficacy Population	116 (80.6)
Primary Reason for Discontinuation n (%)*:	
Adverse Event	3 (2.1)
Lost to Follow-Up	5 (3.5)
Non-Compliance with Study Drug	2 (1.4)
Protocol Violation	1 (0.7)
Withdrawal of Consent	8 (5.6)
Hematocrit > 54%	3 (2.1)
Other	5 (3.5)

Source: Figure 2, page 38 and Table 3, page 39, Study CLAR-12011 report and Statistical Reviewer's listing.
* With respect to number of subjects who took study product.

The majority of subjects was Caucasian (79.2%) and was less than 65 years of age (79.2%). Overall, subjects had a mean age of 54.8 years and a mean screening serum total testosterone concentration of 208.6 ng/dL. The type of hypogonadism is distributed as follows: 46 subjects (31.9%) had primary, 14 subjects (9.7%) had secondary, 72 subjects (50%) had combined/undefined, and 12 subjects (8.3%) had unknown type.

The safety population included 144 subjects who took study drug. The efficacy population included 116 subjects, 28 subjects (19.4%) less than the safety population, and the pharmacokinetic population included 133 subjects, 11 subjects (7.6%) less than the safety population.

Of the 144 subjects in the safety population who took study drug, 28 did not have a serum T C_{avg} on day 114. Of these 28 subjects, 17 did not have sufficient pharmacokinetic data to calculate serum T C_{avg} on day 114 and 11 subjects had no post-baseline data (see Table A.1 in Appendix).

Of these 11 subjects with no post-baseline data, seven subjects discontinued after 30 days or less of treatment and four subjects discontinued after 30 days of treatment (33, 38, 56, and 60 days). Reasons for discontinuation were withdrawal of consent (5 subjects), lost to follow-up (1 subject), adverse event (2 subjects), hematocrit greater than 54% (1 subject), protocol violation (1 subject), and other reason (1 subject).

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Overall, about 17% of all subjects did not complete study due to withdrawal of consent, lost to follow-up, other reasons, adverse event, or hematocrit greater than 54%. These reasons are why there is no day 114 data for these 17% of all subjects, who make up the majority of the 19.4% of subjects with missing day 114 data.

3.2.4 Study CLAR-12011 Results and Conclusions

Primary Efficacy Endpoint

This reviewer has verified the Applicant's pre-specified primary efficacy results, presented in Table 3.3, based on the percentage of subjects with a serum total testosterone C_{avg} in the normal range at day 114 in the efficacy population.

Table 3.3
Study CLAR-12011: Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [≥ 300 ng/dL and ≤ 1000 ng/dL] at Day 114 (Sponsor Efficacy Population*)

Treatment Group	n	Normal Level	Percentage (95% C.I.)
Testosterone Undecanoate	116	87	75.0 (66.1, 82.6)

Source: Statistical reviewer's calculations.
* Efficacy population includes only those subjects with a serum total testosterone C_{avg} value at Day 114.

Efficacy was demonstrated for the pre-specified analysis with the percentage of subjects with a serum total T C_{avg} level within the normal range at day 114 of 70.8% (102 of 144 subjects) with 95% CI of 62.7% to 78.1%.

Post Hoc Sensitivity Analyses of Primary Efficacy Endpoint

The results of post hoc sensitivity analyses, to determine the consistency of the efficacy results after accounting for a 19.4% missing data rate, are presented as follows: this statistical reviewer's results in Table 3.4 and the Applicant's results in Table 3.5. The methodology used for these analyses were described in Table 3.1.

Table 3.4
Study CLAR-12011: Applicant's Post Hoc Sensitivity Analyses Results Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [≥ 300 ng/dL and ≤ 1000 ng/dL] at Day 114

Analysis (Analysis Population)	N	Normal Level (n)	Percentage (95% C.I.)
Worst Case (PK)	133	87	65.4 (56.7, 73.4)
LOCF (PK)	133	99	74.4 (66.2, 81.6)
MMRM with Multiple Imputation (PK)	133	99*	74.8 (66.9, 82.7)
MMRM with Multiple Imputation with demographics (Safety)	144	105*	73.1 (65.2, 80.9)

Source: Response to Information Request submission dated August 12, 2014, supporting document #17 (eCTD # 16), Summary of Sensitivity Analyses table on page 11 of 15 of the Memorandum from Statistics Collaborative
* These are approximate numbers.

Table 3.5
Study CLAR-12011: Statistical Reviewer's Post Hoc Sensitivity Analyses Results Percentage of Subjects with Serum Total Testosterone Level in the Normal Range [≥ 300 ng/dL and ≤ 1000 ng/dL] at Day 114

Analysis (Analysis Population)	N	Normal Level (n)	Percentage (95% C.I.)
LOCF (Safety)	144	102	70.8 (62.7, 78.1)
Worst Case (Safety)	144	87	60.4 (51.9, 68.5)

Source: Statistical reviewer's calculations.

For any post hoc sensitivity analysis conducted to account for missing data in either the safety or pharmacokinetic population using various statistical methods (MMRM with Multiple Imputation, LOCF, or

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worst case scenario), all point estimates for the percentage of subjects with normal serum T C_{avg} are consistently below the 75% threshold. All these post hoc sensitivity results differ from the pre-specified results, which was exactly the threshold value of 75%.

3.3 Evaluation of Safety

For information about the evaluation of safety, refer to the clinical evaluation of safety section.

4. FINDINGS IN SUBGROUP POPULATIONS

No subgroup analyses by gender or geographic region were necessary because all subjects were men and the study was conducted in the United States. There were too few non-Caucasian subjects (< 21%) and too few subjects less than 65 years (< 21%) to conclude if the efficacy endpoint was similar by race or age group. The clinical reviewer did not identify any additional subgroup of interest for statistical review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

One statistical issue was identified in this submission. The pre-specified primary efficacy analysis was based on the completer population that did not include 19.4% of subjects (28 of 114 subjects) who took study drug but did not have a serum total testosterone C_{avg} value at the time point of interest (Day 114).

Not including these 28 subjects in the denominator when calculating a percentage biases the value towards a more favorable result. Overall, about 17% of all subjects did not complete study due to withdrawal of consent, lost to follow-up, other reasons, adverse event, or hematocrit greater than 54%. These reasons are why there is no data for these 17% of all subjects, who make up the majority of the 19.4% of subjects with missing data.

This reviewer conducted two post hoc sensitivity analyses using the safety population to assess the impact of missing data on the consistency of the efficacy results. The Applicant also submitted five additional sensitivity analyses in different analysis populations and based on different methodologies in response to the Agency's request to account for the missing data. Sensitivity analyses are important for this product because of the extent of missing data (19.4%) and because the pre-specified primary analysis result in the completer population is exactly the threshold value used to demonstrate efficacy, which needs to be re-evaluated to determine how it is affected by the missing data.

5.2 Collective Evidence

The one submitted study does not provide evidence demonstrating the efficacy of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism based on the proportion of men who achieved total serum testosterone levels within the normal range. The pre-specified analysis in the completer population achieved success but all post hoc sensitivity analyses to account for missing data did not achieve success.

The evidence is based on achieving total serum testosterone levels within the normal range after 114 days of treatment in at least 75% of men with the lower bound of the 95% confidence interval for the estimate of the proportion of men achieving the total serum testosterone levels within the normal range no less than 65%. The normal range of total serum testosterone level is defined as ≥ 300 ng/dL and ≤ 1000 ng/dL.

The proportion of men with normal total serum testosterone levels was within the success criteria based on the pre-specified analysis using the completer population. This analysis in completers did not include 28 of 144 subjects (19.4%) who did not have total serum T level values at the primary time point of day 114. All post hoc sensitivity analyses conducted to account for missing data did not achieve the pre-specified point estimate success criteria of 75%.

5.2 Conclusions and Recommendations

The one submitted study does not provide evidence demonstrating the efficacy of oral testosterone undecanoate capsules for the treatment of adult male hypogonadism based on inconsistent results between the pre-specified analysis and various post hoc sensitivity analyses conducted to account for missing data.

Reference ID: 3638702

APPENDIX

Table A.1
Study CLAR-12011: Subjects Who Took Study Treatment but Did Not Have Day 114 Total Serum T C_{avg} Data
(Shaded Rows are for Subjects Who Did Not Have Any Post Baseline Total Serum T C_{avg} Data)

Subject ID	LOCF Time Point Used	C_{avg} (ng/dL)	Normal Range?	Days Drug Taken	Reason for Study Discontinuation	Days in Study
(b) (6)	Baseline	277	N	27	Withdrawal of consent	43
	Day 72	421	Y	114	Withdrawal of consent	118
	Baseline	194	N	28	Withdrawal of consent	28
	Day 72	626	Y	112	Withdrawal of consent	113
	Baseline	252	N	15	Other (Prohibited medication not adequately washed out)	16
	Screening	217	N	8	Hematocrit > 54%	11
	Day 72	254	N	88	Lost to follow-up	119
	Day 72	288	N	108	Lost to follow-up	125
	Day 30	394	Y	33	AE (Worsening of hypertension)	62
	Baseline	41	N	60	Withdrawal of Consent	81
	Day 30	633	Y	89	Other (non-compliance with study visits)	90
	Day 72	702	Y	98	Non-compliance with study drug	99
	Day 72	430	Y	97	Non-compliance with study drug	122
	Day 72	462	Y	101	Hematocrit of > 54%	102
	Baseline	470	Y	4	AE (Heart palpitations)	7
	Day 72	265	N	114	Other (Subject out of country)	114
	Baseline	180	N	10	AE (Elevated serum calcium of 10.4)	19
	Baseline	236	N	38	Withdrawal of consent	38
	Day 72	327	Y	114	Other: Unable to locate adequate blood collection site	114
	Baseline	502	Y	56	Withdrawal of consent	56
	Baseline	565	Y	33	Lost to follow-up	69
	Baseline	256	N	6	Protocol violation (Hct > 48%, eligibility criteria not met)	8
	Day 30	298	N	74	Withdrawal of consent	75
	Day 72	716	Y	116	Lost to follow-up	124
	Day 72	400	Y	124	Other: subject could not finish v6 because could not get the day off at work.	125
	Day 72	759	Y	96	Hematocrit of > 54%	98
	Day 72	771	Y	86	Lost to follow-up	124
	Day 72	234	N	113	Unknown	

Source: Statistical Reviewer's listing.
* Shaded rows indicate the 11 subjects who took study drug but did not have any post-baseline data

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/s/

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